Matière
à débattre & décider

Emergence of infectious diseases

Risks and issues for societies

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1. Biogeography and the ecology of emerging infectious diseases

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A major epidemic of Ebola occurred in West Africa in 2014, causing more than 11,000 deaths by the time the outbreak ended in mid-2016. This extremely deadly haemorrhagic fever of viral origin created a serious regional health crisis and led to fears that it would spread across the globe. In its early days, and for many months, the epidemic received little attention from international institutions, particularly the World Health Organization (WHO). The turning point came when a few cases appeared in Western countries, most of which were health workers who had been repatriated after being infected when treating patients. The risks of introducing and spreading the virus in Western countries became very significant when secondary infections, once again affecting health workers, occurred in Spain and the United States. The health crisis suddenly shifted from a regional concern to a global one.

Ebola is an illustrative example that can be used to examine fundamental questions about the ecology and epidemiology of emergence. This disease is caused by infection from a virus carried by bats. Human contamination occurs not only by handling infected bats, which is assumed to be the cause of the first case of the West African epidemic, but also through contact with wild animals, primates or antelopes infected with the virus that are hunted or sold as bushmeat. But large epidemics like the one observed in West Africa or previous epidemics in Central Africa are the result of contact transmission between sick people and healthy individuals (more specifically, when caring for the sick or when coming in contact someone who has died of the disease). The disease is then transmitted directly between people, with no need for transmission from the animal reservoir until transmission is under control and the virus persists only in bats.

This epidemic raises a number of questions about the ecology and geography of emergence. What are these emerging pathogens? What are their origins? Why are bats so frequently mentioned? What is the link with humans: who infects whom and how? Are there any geographic 'hotspots' of emergence? Is Africa unique, or the tropics in general? Is this Ebola health crisis in West Africa a bat problem, or is this health crisis more indicative of an environmental crisis coupled with a social crisis?

An emerging infectious disease is defined by Steven Morse (1995) as an infection that has recently appeared in a population or that has existed before, but whose incidence or geographic range is increasing rapidly. We should note that this definition also relates to the rise of bacterial resistance to antibiotics. But how is this concept of emergence, derived from the work of scientists such as Steven Morse, supported by comparative studies in global epidemiology?

Human history has been profoundly marked by emerging infectious diseases such as the Black Death in the Middle Ages or the Spanish flu at the end of the First World War. Infections also contributed to the decimation of Native American and Pacific Islander populations following European colonization (McNeill, 1976). These emerging diseases are ever present in our collective experiences. The emergence of the AIDS, SARS, avian influenza (H5N7), swine flu (H1N1), West Nile virus and the recent Ebola virus in West Africa remind us that infectious diseases, still a global risk for world health, maintain a hold on our imaginations. Are these recent emerging pathogens new or different from the emergence and epidemics such as bubonic plague, smallpox or typhus that have occurred throughout human history?

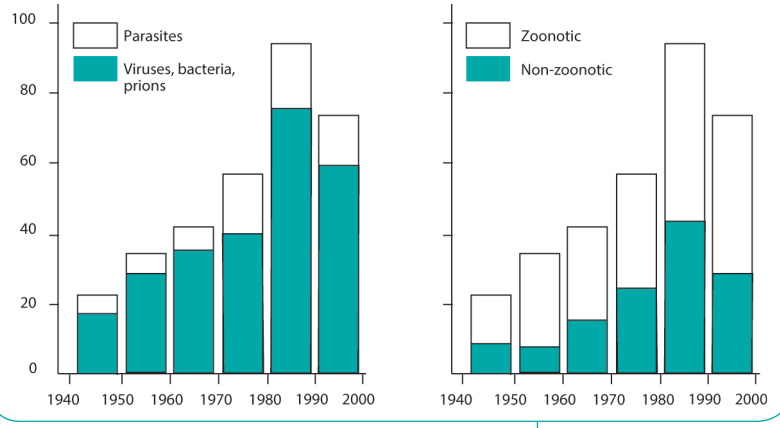
Characteristics of emerging infectious diseases

The human species is infected with a large number of pathogens, undoubtedly making us the most parasitized species on Earth. More than 1,400 species of parasites and microbes have been listed as pathogenic in humans (Cleaveland *et al.*, 2001) and, of these, more than 60 percent are of zoonotic (i.e., animal) origin. The percentage of zoonotic pathogens observed in all infectious diseases affecting humans is the same as the percentage observed for the newly emerging infectious diseases. Thus, emergence does not present an original character within the total diversity of infectious diseases that have and still continue to affect humanity.

The study by Jones *et al.* published in *Nature* in 2008 will serve as a guide for the ecological and epidemiological analysis of emergence and improve understanding of the dynamics. Since its publication, this study has been cited more than 2,000 times in scientific literature, demonstrating both the interest of the subject for the scientific community and how original it is. This study contributed to the effective implementation of several programmes by the United States Agency for International Development (USAID). These programmes aimed to detect and prevent emerging diseases in their likely places of emergence. However, we will come back to this point when discussing the geography of emergence. This study also provided the scientific basis for the One Health initiative led by the United Nations Organization for Food and Agriculture (FAO), the World Organisation for Animal Heath (OIE) and the World Health Organization (WHO).

In their study, Jones *et al.* (2008) showed a significant increase in the number of emerging infectious disease (EID) events from 1940 to 2000 (Fig. 1). They then noted that the agents

Figure 1. Evolution of the number of emerging infectious diseases (EIDs) from 1940 to 2000, according to the type of pathogens (parasites or viruses and bacteria) (left) and according to the type of zoonotic transmission (involving wild or domestic animals) or non-zoonotic (environmental, vectors without animal reservoirs, direct human-to-human contact) (right).



Adapted from Jones *et al.*, 2008.

responsible for these EIDs are mostly viruses and bacteria. Parasites, i.e., worms (such as nematodes or tapeworms) and protists (such as malarial agents) account for a minority of these newly emerging agents. Finally, more than 70% of these EIDs originated from animals (mainly wild).

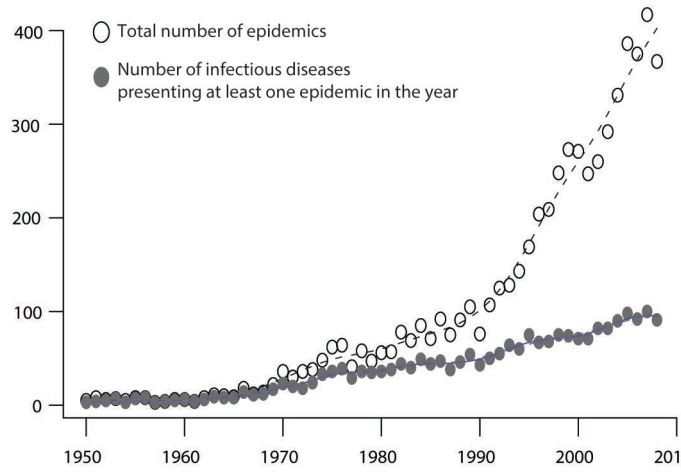
The Jones *et al.* (2008) study focuses on three characteristics of these EIDs: (1) there is an epidemic of EIDs (2) mainly due to microbes (viruses and bacteria), (3) many of which originate in wild animals.

In trying to answer the question as to whether these EIDs are different from the infectious diseases that have and still do affect human populations, we must recognize that the number of infectious diseases that are present in a country or a geographic region and the number of infectious disease outbreaks are two distinct issues.

The number of diseases, or the burden of infectious diseases, is a static measurement that corresponds to the sum of medical knowledge of a given country or region. Although it obviously takes into account past eradications or new emergences, the number of diseases is a measure of how endemic infectious diseases have become in a geographical area where infectious agents may circulate without significant epidemic outbreaks.

The number of epidemics is a dynamic and temporal measurement, which shows the number of remarkable epidemiological events at a given moment or over a given period.

Figure 2. Evolution of the number of epidemics of infectious diseases in the world from 1950 to 2010: total number of epidemics in the year (upper curve in black), number of infectious diseases presenting at least one epidemic in the year (lower curve in grey).



Adapted from Morand, 2015.

Detecting and reporting an epidemic event requires a public health service that is able to monitor, identify and carry out national and international outbreak notifications. The quality of the public health service depends on the financial resources allocated to it and, indeed, there is strong correlation between the number of epidemics affecting a country and its GDP or per capita expenditures for the public health system. The wealthier a country, the more it is able to detect, characterize and report different epidemics internationally, regardless of the number of diseases present in the country. This bias has been taken into account in all published studies (including that of Jones and his colleagues).

Analysing trends in the global epidemiology of infectious diseases has been the subject of several studies, most having used the online database GIDEON (which includes data from the WHO). The trends in all global infectious disease outbreaks are similar to those that are limited to EIDs alone (Smith *et al.*, 2014, Morand *et al.*, 2014c). Global disease outbreak trends are also increasing exponentially (Fig. 2). There is an epidemic of epidemics of all types of infectious and parasitic diseases.

Although less dramatic than the total number of outbreaks, there is also a significant increase in infectious diseases with at least one epidemic in a year. This indicates a rise in different kinds of infectious diseases, including EIDs, presenting an outbreak over the last 60 years. Finally, EID events share two characteristics: more than 60% of these outbreaks are from zoonoses, and the causative agents are mostly viruses and bacteria.

At least two studies have explored these epidemic patterns regionally in Europe and Asia Pacific (Morand and Waret-Szkuta, 2012; Morand *et al.*, 2014a). They also showed the same exponential increase in infectious disease outbreaks. These two regions, which have different socioeconomic and environmental profiles, with high intra- and inter-country variability, showed strikingly similar trends and patterns in the dynamics of their infectious diseases. This raised the question of what common factors might explain such similarity.

What are these emerging pathogens?

The increase in not only emerging but all infectious diseases in recent decades mainly concerns bacteria and viruses. For tropical medicine, this is a major change. Tropical medicine has long focused on parasitic diseases caused by helminth worms (schistosomiasis, tapeworms and intestinal strongyles) or protists such as trypanosomes responsible for sleeping sickness and Chagas disease. Although these diseases are still public health problems, they are not in the scientific mainstream of emerging infectious diseases or even in the global dynamics of epidemics (McIntyre *et al.*, 2011). A new medical field has been created for 'traditional' tropical diseases that are losing the attention of health policies, donors and scientists while new journals are cropping up for these 'neglected tropical diseases'. Some of these neglected infectious diseases are re-emerging (such as leptospirosis), suggesting that the 'emerging' label attached to an infectious disease is first and foremost an indication of emerging scientific, social and political interests.

Going back to the definition of emergence given by Steven Morse, for an infectious disease to become emerging, it must be new and/or expand its geographical range. Starting with the new aspect of an infectious disease, the development of molecular biology must be considered along with its applications in the biomedical and epidemiological field with new rapid and less expensive methods to detect and characterize pathogens (still requiring significant technical advances). While medical or veterinary parasitology still relies on macroscopic characterization of parasites, such as the use of the optical microscope, the development of molecular methods has helped refine the distinction of certain species (within species complexes) or genetic variability between different circulating strains. Microbial infectious diseases, i.e., bacterial and virologic, greatly benefited from the rapid growth of these new molecular techniques. The coronavirus responsible for SARS is the best example of the rapid detection and characterization of a new infectious agent. New species and strains have been and can be characterized by these new tools very quickly. These advances led to virtual real-time sequencing and analysis of the circulating strains of the Ebola virus in West Africa. A new profession appeared: virus or 'bug hunter' as defined by Nathan Wolfe.

Paradoxically, this scientific and technological development is part of the rise in EIDs. Emergences are easier to see and different emergences are better characterized because of the financial, technological and scientific resources available to detect them and identify the causative pathogens. Accordingly, any analysis of temporal epidemiological trends

must take into account the means that a country or the international community could use to monitor epidemics and characterize the pathogens that are circulating and emerging.

The rise of new high-throughput sequencing techniques also makes it possible to carry out an unbiased investigation of the entire community of microbes and parasites that an individual or an animal species harbours. This is what is referred to as the microbiome (all bacteria living on the skin or in the digestive tract), the virome (all viruses including pathogens and retroviruses) and the parasitome (all parasites). Brand new explorations of living beings are now possible, similar to the great expeditions conducted by museums of natural history. However, the consequences for societies are very different. Once again the example of bats and the first studies of their viromes provide a good example.

Based on characterization of part of a bat's virome, a species of flying fox that is a reservoir of many emerging viruses, Anthony *et al.* (2013) statistically extrapolated their results to the potential number of all viruses circulating in mammals. Without going into the many methodological and statistical biases of such work, the authors arrived at a number of more than 320,000 viruses waiting to be discovered in mammals.[1] All of these 'possible' viruses were presented as 'potential' sources of future EIDs. But the authors concluded that the complete characterization of these viruses (it would multiply by a factor of 60 the number of known characterized viruses) would cost $6.3 billion, a "small fraction of the cost of many pandemic zoonoses". This work and these quotations have been widely reported by the international press (the BBC, *Le Monde* and major American networks).

A year later, in 2014, an Ebola outbreak erupted in West Africa. Would the characterization of all mammalian viruses proposed by Anthony and his collaborators have helped prevent and contain this epidemic? Are bats the culprits of this epidemic, and if so, would a wildlife surveillance strategy or even monitoring of bushmeat hunters as promoted by Nathan Wolfe (2011) have prevented and contained the epidemic?

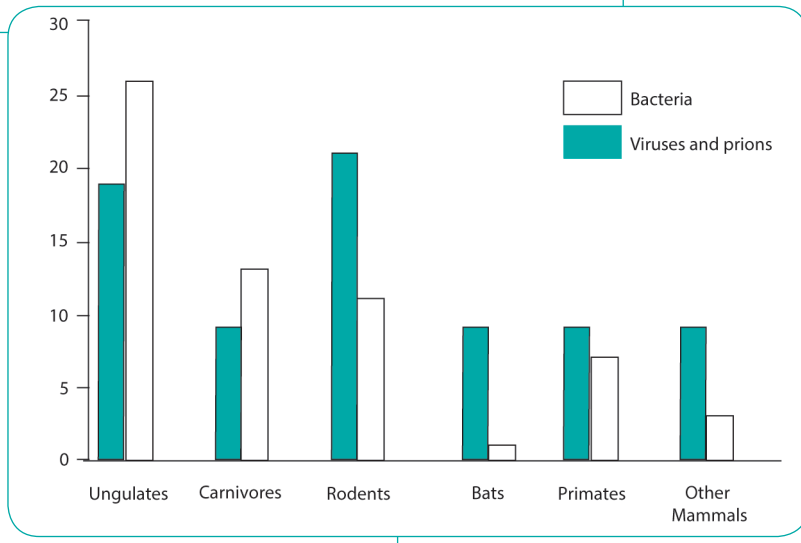
What are the animal reservoirs of these new emerging infectious diseases?

Woolhouse *et al.* (2005, 2008) have characterized the reservoirs of these emerging parasites and microbes. Their articles again show that viruses and bacteria are the main agents at the origin of emerging infectious diseases, and that emergences are overwhelmingly zoonoses. But the main interest of these studies is the characterization of animal reservoirs of zoonoses (Fig. 3).

First of all, ungulates (hooved animals such as cattle, horses, goats and sheep) appeared as major reservoirs of new emergence, but carnivores (dogs, mostly cats) also play an

1. It should be noted that over 5,000 virus species have been fully characterized and that the total estimated number of viruses on Earth is 10^{31} (a one followed by 31 zeros!), with most being bacteriophages, viruses that infect bacteria.

Figure 3. Characterization (number) of emerging zoonotic disease reservoirs.



Adapted from Woolhouse and Gowtage-Sequeria, 2005.

important role in the spread of emerging infectious agents. In the case of wildlife, rodents are the reservoir group that contributed most to new emergence, followed by primates and bats.

It should be noted that certain rodents responsible for disease transmission are long-time human commensals (such as black rats, brown rats or house mice) or newly kept as pets (e.g., prairie dogs or Gambian pouched rats). For example, leptospirosis caused by a bacterium that lives in the environment re-emerged globally from the 1990s with rodents and domesticated animals as reservoirs. Despite the many people at risk and infected – mainly the poor in developing countries – this disease remains under the radar.

While bats are stigmatized when major health crises arise, such as during the last Ebola outbreak, they are only responsible for a relatively small proportion of these emergences. Why do they receive so much attention?

What are the emerging viruses in bats?

Bats receive considerable attention from health services as well as scientists. Understanding disease emergence related to these animals requires studying modes of virus transmission from bats to humans. Transmission is rarely direct and most often involves other wild or domesticated animals.

Although human rabies cases are mostly the result of a bite from a rabid dog, the lyssavirus that causes this frightening and fatal zoonotic disease originates in bats (Johnson *et al.*, 2010). Carnivores are secondary carriers of this virus, which also infects many other animals. In the early 1900s in Brazil, 4,000 cattle and 1,000 horses and mules died of paralytic rabies. Bats, which were actually infected with the rabies virus, had been observed near these animals trying to bite them. This was the first causal link between bats and viral diseases (Halpin *et al.*, 2007). The rabies virus was then isolated from an insectivorous bat in the United States in 1953. A few cases of human rabies have been described following a bite by a bat, but they remain marginal compared to bites by dogs.

With regard to Ebola, there is not just one Ebola virus, but several species that have been responsible for multiple outbreaks in Central Africa and the most recent one in West Africa. The first emergence dates to 1976, with the Zaire Ebola species, followed by the Sudan, Taï Forest and Bundibugyo species. Transmission is often the result of handling bushmeat at the markets, as in the case of primates infected in markets in the Democratic Republic of Congo. High mortality and human-to-human transmissions make Ebola a high-risk zoonosis. Bats are the reservoirs of these Ebola viruses.

Reston virus (RESTV), also in the Ebola group, was discovered in macaques at Hazleton Laboratories in the United States in 1989. This virus is non-pathogenic for humans, but dangerous for monkeys. It has been found in macaques in Southeast Asia.

The first infections from the Marburg virus (named for a city in Germany) involved researchers from a pharmaceutical company who became ill following kidney cell manipulations taken from green monkeys imported from Uganda. Epidemics were then reported in the Republic of Congo in 1998, in East Africa in 2000, in Angola in 2004 and 2005, and in Uganda in 2014. The reservoir is a dogfish.

Some emerging viruses belong to the Paramyxoviridae family (Wang *et al.*, 2008). Viruses in this family are the agents of measles and mumps in humans, and Newcastle disease, distemper and rinderpest in domesticated animals. Three new paramyxoviruses of bat origin have emerged since 1994 in Australia, South and Southeast Asia and the Arabian Peninsula. These are the Hendra virus (HEV) isolated from horses and humans infected in Australia in 1996, the Nipah virus (NiV) in humans and pigs in Malaysia in 1999, and the Menangle virus (MENV) in pigs in Australia in 1997.

The various Hendra virus epidemics in Australia all affected horses and humans who were in direct contact with infected horses. Large frugivorous bats are the reservoirs of this virus.

Nipah virus outbreaks occurred in Malaysia in 1998, where pigs raised as livestock and humans were infected. In Singapore, human infections occurred in slaughterhouse workers where pigs were imported from the contaminated areas of Malaysia. Flying foxes and small insectivorous bats are NiV reservoirs. Other Nipah virus outbreaks occurred in Bangladesh between 2001 and 2005, and in India in 2001. The infections are believed to be directly from bats (flying foxes) with proven human-to-human transmissions.

The Menangle virus emerged in Australia in 1997 at a large intensive pig farm near Sydney, with two human cases associated with swine disease. Bats remain reservoirs for this virus.

Four Coronaviridae viruses cause anodyne human diseases, but two other virus species from this family are responsible for two major health crises: Severe Acute Respiratory Syndrome (SARS), with more than 8,000 people infected in around 30 countries, and the Middle East Respiratory Syndrome (MERS). In 2002, a coronavirus emerged in Guangdong Province, China, which was responsible for the SARS epidemic reported to be related to small carnivores called civets sold in bushmeat markets in southern China. Wild reservoirs of this virus are bats (Moutou 2007). In 2012 in the Arabian Peninsula, the first human case of infection with a new coronavirus causing a respiratory syndrome, MERS-CoV, was identified. Human-to-human transmissions have been identified with imported cases in Europe, Asia and the United States. The reservoirs are small insectivorous bats, but human infection occurs through dromedaries infected with the virus.

There are several key points to take away from this brief summary of emergences. First, bats are the reservoir of highly lethal infectious diseases that have emerged in recent decades, leading to major health crises such as SARS, Nipah, MERS-CoV and the recent Ebola outbreak. However, direct viral contamination between bats and humans is rare, and happens through an intermediate species like primates, carnivores, horses or dromedaries. These animals are close to humans, either phylogenetically, such as primates with whom we share many diseases and parasitic infections, or because they have domesticated for millennia. Finally, two main geographical areas host these emergences: Africa and Asia Pacific. We will return to the geography of emergence, but will first look at the role of domesticated animals.

What roles do domesticated animals and pets play in emergence?

Human interactions with animals appear essential to understanding the human epidemiological environment. Studies have examined the ecological, historical and biogeographical associations of humans with their parasitic and infectious diseases (McNeil, 1976; Diamond, 1997; Wolfe *et al.*, 2007), and some have specifically focused on the importance of animal domestication.

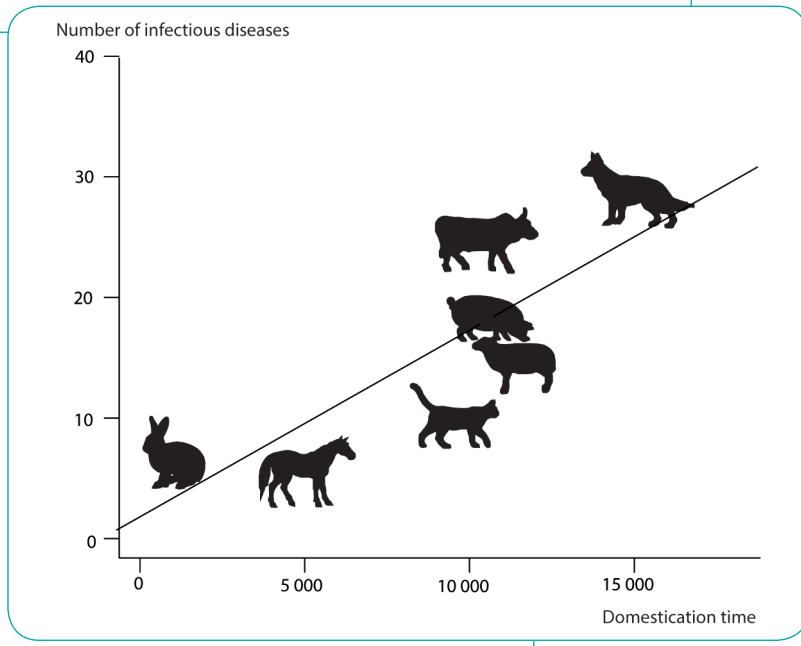
Archaeological studies show a rapid and large-scale domestication of animals starting around 12,000 years ago, during an intense wet climate phase. The main animal domestication centres are located in the Middle East and Central, South-west, South and East Asia. Few mammal species were domesticated in Africa (the donkey in the Horn of Africa), Western Europe (the rabbit in the Iberian Peninsula) and the New World (llamas and the Guinea pig). Animal domestication associated with the Neolithic Revolution significantly altered human nutrition just as the domestication of plants changed land use. The consequences were considerable for human and animal health, leading the Neolithic populations to have a significantly poorer health status compared to the hunter-gatherer populations that preceded them. Similarly, the initial stages of domestication resulted in a deterioration of

the health of these animals. New and lasting interactions between humans and animals, associated with the stresses of domestication, have favoured the emergence of disease.

In his book *Plagues and People* (1976), historian William McNeil was the first to hypothesize that infectious diseases were major, albeit contingent, agents in human history (an assumption picked up and later popularized by Jared Diamond). McNeil suggested a positive relationship between the time of domestication and the number of diseases that humans share with each domestic species. A statistical analysis of this hypothesis using novel sources for domestication or infectious diseases and updated data on the dates and origins of domestication confirms McNeil's idea. The number of pathogens shared between humans and each domestic species is proportional to the time since its domestication (Morand *et al.*, 2014d) (Fig. 4). A long period of interaction is necessary for the number of infectious diseases shared between animals and humans to increase.

To gain a better and more comprehensive view of the interactions amongst pathogenic agents, humans and domestic animals, a network analysis (like those widely used in

Figure 4. Relationship between the domestication time of major domesticated mammals and the number of infectious diseases shared with humans.



Adapted from Morand *et al.*, 2014d.

epidemiology) can help determine the domestic species that share the most pathogens between humans and all domestic animals. These central species in the network are infected with many pathogens that also infect myriad other species in the network. The oldest domesticated species carry the most zoonotic agents that they then share with humans and, more recently, other domesticated species.

These statistical observations underscore that time and close proximity with livestock and other domesticated animals are essential factors in the construction of the epidemiological environment of human societies. However, this type of analysis does not take into account reservoirs and new targets of these agents. Doing so requires phylogenetic studies, which show that cattle and pigs are the source of many infectious or parasitic agents for humans, such as roundworms in wild boars very early in their domestication. However, domesticated animals were in turn affected by pathogens from humans such as *Mycobacterium bovis*, a bacterium from a strain of the human tuberculosis agent *Mycobacterium tuberculosis* (Smith *et al.*, 2009). Finally, different domesticated animals may exchange pathogens amongst themselves, as in the case of influenza viruses.

There are two essential aspects to consider from these phylogenetic studies. First, it takes time and close proximity (or numerous repeated contacts) for an infectious agent to adapt to humans or to a community of humans and domestic animals. This phenomenon concerns mainly the parasites and pathogens of non-human primates which, because of their close evolutionary history, have advantages – particularly physiological and biological – to infect humans (such as AIDS viruses, or Plasmodium in African and Asian primates). Second, it is important to note the importance of certain domesticated animals for the maintenance and transmission of pathogens by operating as epidemiological 'bridges'. Emergent (but also non-emergent) influenza viruses illustrate this with domestic or wild bird reservoirs, and animals such as pigs allowing the rearrangement of viruses, thus promoting their 'humanization' and their potential to infect humans.

These observations also apply to pathogens from wildlife, such as the emergence of viruses from bats. The vast majority of emergences of viruses associated with bats are due to viral amplifications and adaptations in domesticated animals such as horses, pigs, dromedaries, dogs or primates.

What is the geography of emergence?

The recent Ebola outbreak in West Africa appears to be the manifestation of Pulitzer Prize-winning journalist Laurie Garrett's worst prediction from her book *The Coming Plague* in 1994: humans would contract new pathogens in the tropics – environments rich in animal biodiversity – such as Equatorial Africa. The risks of emergence are linked to the increase in local, regional or international human mobility coupled with a change in the natural environment due to increasing demographic pressures.

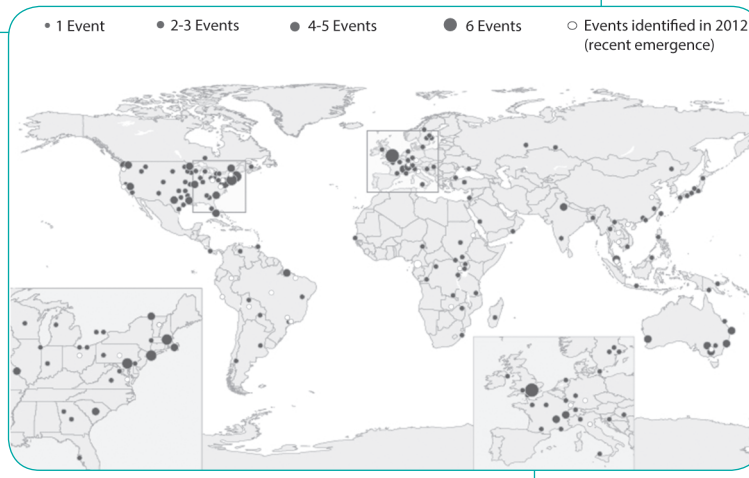
A new infectious disease of local origin would have its chances of emergence – or even possible pandemic success – reinforced by globalization. Examples include SARS, avian and swine

flu, and the human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS). Our collective memory remembers the epidemics of bubonic plague in the Middle Ages, which spread due to regional and international trade and mobility as well as socioeconomic and climatic conditions that weakened societies of the time.

Is it possible to depict a biogeography of emerging infectious diseases? The article by Jones *et al.* (2008) further illustrates this point. The authors provided two maps, which were also widely repeated and commented on in the scientific literature and international organizations such as the FAO. The first map pinpoints the localities of the emergence of these new infectious diseases while the second map uses statistical models to extrapolate the probable geographical areas where the next infectious diseases might emerge. These maps are interesting for several reasons.

The map of locations of past emerging infectious diseases shows that Europe and the United States are the main regions of the Western World with EIDs over the last 60 years (Fig. 5). Other developed countries such as Japan and Australia are also clearly visible as hotspots of past EIDs. A second observation is that the world's largest cities, including those in emerging economies, were affected by past EIDs. Such a map suggests that Western societies are at risk for emerging diseases as well as all major world cities, including those in the Global South. The entire world dominated by the Western model of economic development seems to a 'target' of EIDs.

Figure 5. Map showing the location of emerging infectious diseases from 1940 to 2000, depicted in Fig. 1.



Adapted from Jones *et al.*, 2008.

A second map, published in Jones *et al.* (2008), provides an interesting perspective. This map presents potential future areas of emergence for infectious diseases of zoonotic origins (wild and domesticated animals). Western developed countries and large cities are hotspots of potential new EIDs of zoonotic origins, but new regions appear, especially South and East Asia. The map points to the newly emerging economies of South Asia, characterized by dense populations, agricultural intensification, rich biodiversity and an increasingly strong integration into the world economy.

The African Great Lakes area around the East African Rift as well as southern Nigeria also appear as hotspots of potential new EIDs. This can be explained by their rich biodiversity and the densely populated areas of these African regions. Note that West African countries affected by the 2014 Ebola outbreak are only slightly highlighted. Finally, South America does not appear as a hotspot for future emerging zoonotic diseases.

From the article by Jones and his colleagues, the conclusion can be drawn that emerging diseases start in the tropical world, and especially Asia and Africa, but that ultimately developed or emerging economies suffer the consequences. This explains the differences between the locations of reported EIDs (in developed and emerging economies) and the locations of wildlife-related infectious disease risks (in developing countries, with both high biodiversity and dense populations). Active policies focusing on researching conditions prone to the emergence of infectious diseases and identifying and detecting emerging pathogens, coupled with prevention strategies in these potential EID hotspots, would avoid having to manage health crises in both developing countries and the developed world. Such approaches have been included in USAID programmes and publications by international UN agencies (such as the FAO).

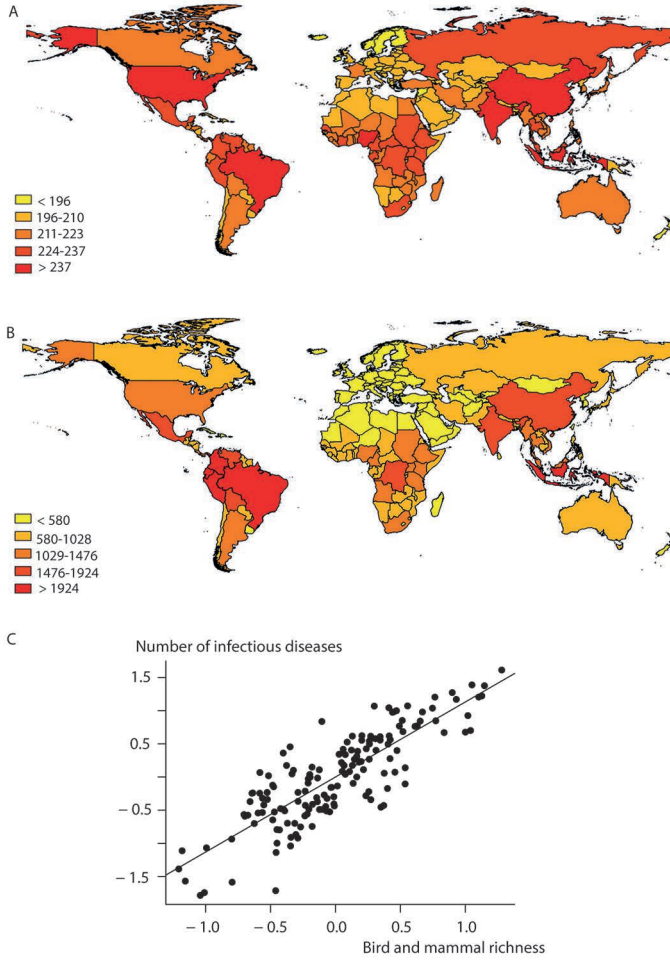
With regard to the global epidemiological data, a number of questions can be raised. For example, what is the geography of infectious diseases and the parasitic burden of the human species? How can it be explained?

What is the geography of infectious diseases and parasitic burden?

Human pathogens are not distributed randomly across the planet. The richness of infectious diseases increases from high latitudes to the tropics (Guernier *et al.*, 2004, Dunn *et al.*, 2010, Morand *et al.*, 2014) (Fig. 6A). Interestingly, this latitudinal gradient follows that of general biodiversity. The richness of bird and mammal species is also higher in the tropics than in the northern latitudes (Fig. 6B). This fact has been known since the inception of biogeography and continues to generate questions about the ecological, climatic or energetic mechanisms responsible for this biodiversity gradient.

Interestingly, a positive correlation is shown between richness in birds and mammals species and richness in human infectious diseases. A country with a high biodiversity of vertebrates (birds and mammals) is also home to a wide diversity of pathogens (Dunn *et al.*, 2010, Morand *et al.*, 2014) (Fig. 6C). This observation on a global scale is found at regional scales:

Figure 6. A. Map of infectious disease richness by country. B. Map of species richness of birds and mammals by country. C. Relationship between infectious disease richness and bird and mammal richness by country (data from the GIDEON database).



Adapted from Morand *et al.*, 2014c.

according to two studies performed at a regional level, the richness of infectious diseases correlates positively with the richness of birds and mammals in Europe and Asia Pacific.

More intriguingly, cultural diversity, known to be correlated with biological diversity, also is positively correlated with diversity in infectious diseases. This means that a country rich in biodiversity is a country rich in cultural diversity (often measured by its linguistic diversity) and with a high diversity of infectious diseases.

Studying the mechanisms that explain the diversity of infectious diseases affecting human populations must therefore take into account not only ecology (animal diversity), but also anthropology (cultural diversity). An approach for such research is what can be called the 'socioecological niche' of health, which might find its supporters in both anthropology and ecology. The existence of varied environmental niches enables adaptation, specialization and local diversification for both biological diversity and cultural diversity. Some researchers even identify mechanisms of co-evolution and local co-adaptation of humans and nature (e.g., for natural biodiversity and cultivated biodiversity) contributing to biogeographic entities defined as 'eco-regions' and hotspots of 'bio-cultural diversity' (see the work of Hamond and Maffi, 2002, Maffi, 2005).

The observed relationships between biological diversity and cultural diversity on the one hand and biological diversity and infectious disease diversity on the other have led some authors to focus on searching for causal links between cultural diversity and infectious disease diversity (Fincher and Thornhill 2008). These authors proposed sociobiological explanations, which are beyond the scope of this chapter. However, as emphasized here, studying infectious diseases needs to confront fundamental questions in biology, ecology and anthropology with potentially important policy and philosophical implications.

What lessons can be drawn from this first chapter? First, the pattern and diversity of emerging infectious diseases are not fundamentally different from those of all infectious diseases that have affected and continue to affect human populations. They are mostly zoonoses caused by viruses and bacteria.

Second, emerging infectious diseases are detected in developed countries of the northern hemisphere (and some southern hemisphere countries such as Australia) because these countries have the biotechnological capabilities to characterize them. However, the risks of new zoonotic diseases are most likely located in the intertropical zones (South and South-east Asia, Central Africa), which are hotspots of animal and plant diversity, cultural diversity and infectious disease diversity.

Factors of emergence: climate change, biodiversity, land use and globalization

Studies on emerging infectious diseases attribute their increase to human activities. The explanatory factors are those of ongoing global changes: climate change and its variability, globalization with economic development and international trade, land use

changes including deforestation and associated biodiversity loss, and biological invasions. The impacts of these changes on arthropod vectors, such as the Asian tiger mosquito, are among the most cited examples. EIDs are a phenomenon related to these global changes that is characteristic of a new geological era: the Anthropocene.

There would appear to be a contradiction at this point. The previous section of this chapter showed that rich biodiversity is associated with many human infectious diseases (the statistical correlation observed between the number of birds and mammals and the number of human pathogens). If this is true, how could a loss of biodiversity be associated with an increase in the number of EIDs? The explanation given is that biodiversity loss is associated with more interactions between humans, their domesticated animals and wildlife. Habitat fragmentation and agricultural and livestock intensification affect local biodiversity in terms of both species richness and the composition of animal and plant communities. These phenomena also lead to new contacts between humans and domesticated and wild animals.

A typical example is the emergence of the Nipah virus in Malaysia, where massive deforestation has caused fruit bats to migrate to new areas and food sources, such as date palm plantations. These plantations, located in areas of intensive pig farms producing for the international market, have created conditions for new infectious contacts between bats and pigs, followed by infectious contacts between pigs and humans, both locally in Malaysia and in Singapore, where the pork ends up.

Several studies have also shown that reduced biodiversity at the local level can lead to an increase in prevalence rates and transmission of certain infectious diseases. These studies focused on Lyme disease, West Nile fever, and hantavirus haemorrhagic fevers (Keesing *et al.*, 2010). Note that these three EIDs have affected the United States and were the subject of intense research efforts. The studies explain the success of transmission of a pathogen by a mechanism called ‘dilution effect’.

Dilution effect occurs when the local biological community is enriched with species that are not pathogen reservoirs. Infections of these species are epidemiological dead ends or ‘lost transmissions’ that negatively affect the persistence of the pathogen despite the presence of highly competent reservoir species. The proposed initial mechanism for dilution effect with lost transmission concerns vector-borne diseases. Arthropod vectors are often not very discriminating (such as ticks in Lyme disease or mosquitoes in West Nile fever). The number of their blood meals on non-competent species (they are the ones that do not allow the development of the pathogen) increase with the richness and abundance of these non-competent species in the overall community. These non-competent hosts are unable to ensure the multiplication or transmission of pathogens. A study showed that the human prevalence of infection for West Nile fever is negatively correlated with the species richness of birds. High local bird biodiversity appears to dilute virus transmission due to the presence of many non-competent bird species for the virus development and transmission. This high biodiversity of wild avian fauna reduces human exposure to this virus (Swaddle and Calos 2008).

Other dilution-effect mechanisms have also been proposed for directly transmitted pathogens, often referred to as 'indirect dilution effects'. In this case, it is no longer a question of transmission losses to non-competent species, but of a decrease in the abundance of reservoir (or competent) species. High biodiversity is characterized by many species with relatively low abundance. A highly diverse animal community is therefore composed of reservoir species and non-competent species living in low-density (population) abundance. The effect is reduced efficiency of transmission to the relatively rare competent hosts, as observed in the case of hantavirus hosted by rodents. Highly diverse communities of rodent species are characterized by a low population density of reservoir or competent rodents. Transmission and prevalence of hantaviruses are low, and so are the risks of transmission of these viruses to humans.

Several other studies have provided strong support for the dilution effect (direct or indirect). This has encouraged certain scientists to conclude that biodiversity loss tends to increase pathogen transmission and the incidence of infectious diseases (Keesing *et al.*, 2010). Local biodiversity conditions, species richness and species composition (including reservoir hosts) are believed to be the determining factors in the transmission of zoonoses from wildlife. The loss of biodiversity would be associated with a loss of ability to control or regulate the spread of pathogens in the ecosystem. Accordingly, biodiversity is assumed to provide an ecosystem service for the regulation of infectious diseases.

However, other studies question any positive role of biodiversity on zoonotic disease transmission. The preservation of biodiversity can even lead to increased health risks. The fight against deforestation would lead to an increase in malaria risk in Brazil as suggested by Valle and Clark (2013). Lafferty and Wood (2013) emphasized that considering biodiversity as a protection against wildlife health risks is a "myth" that can be counterproductive to the intrinsic goals of biological conservation. In support of their demonstration, a meta-analysis[2] of a set of studies tested the effect of dilution and found a lack of statistical support for this effect. Additionally, this meta-analysis was not very optimistic in its conclusion on the theoretical power of scientific ecology. The effect of biodiversity on the local transmission of an infectious disease would not be predictable because it is idiosyncratic, i.e., contingent on local conditions, (Salkeld *et al.*, 2013). However, two more recent meta-analyses conducted on a greater number of studies confirmed the statistical existence of a dilution effect (Civitello *et al.*, 2015; Johnson *et al.*, 2015).

The research appears to be quite contradictory, but many of the studies cited above sometimes confused or maintained confusion between disease diversity, disease transmission and disease epidemics. Disease epidemics are characterized by temporal and geographical aspects from local to global (i.e., pandemics), regardless of whether

2. Meta-analyses are statistical analyses of statistical results from various independent studies. They are quite common in the field of biomedicine to compare epidemiological studies.

they concern an emerging infectious disease or not. We should now look at how infectious disease epidemics are linked to global changes and biodiversity.

What are the effects of biodiversity changes on disease epidemics?

A previously cited study on one of the emerging infectious disease hotspots – Asia Pacific – sought to explain how biodiversity could affect the infectious disease epidemics (Morand *et al.*, 2014b). This macro-epidemiological study took into account socioeconomic aspects (population, GDP per capita, public health expenditure), geographical aspects (latitude and country areas), climate factors (precipitation, temperature) and biodiversity (bird and mammal species richness, forest cover, and the number of species of mammals and birds in danger of extinction). Although the number of infectious diseases correlated well with biodiversity, the total number of zoonotic disease epidemics over the 1950–2010 period was positively correlated with the number of endangered mammal and bird species. The number of vector-borne infectious diseases (whose agents are transmitted by arthropods) was negatively correlated with forest cover. These results suggested that zoonotic and vector-borne disease epidemics were associated with biodiversity loss as measured by endangered wildlife or forest cover. These results support the hypothesis that biodiversity regulates the spread of pathogen transmission. However, these results do not explain the underlying ecological and epidemiological mechanisms that should be analysed at local scales.

A key point that should be highlighted is the role of economic development, estimated by GDP per capita. Biodiversity-rich tropical countries are developing by intensifying agriculture and livestock for the needs of local, regional and global markets. The increase in GDP correlates to the environmental impact on biodiversity linked to economic development and integration in the global economy. But the increase in GDP also improves the public health system, which in turn enhances the ability to detect infectious diseases and their epidemics, and lifts the well-being and health of populations. The downside is that economic development, through its impact on biodiversity (richness and forest habitats), favours zoonotic or vector-borne infectious disease epidemics, including the risks of new emerging diseases. The emergence of the Nipah virus in Malaysia as a result of agricultural intensification is one example of this, as is the emergence of zoonotic malaria due to *Plasmodium knowlesi* following the conversion of Malaysian tropical forests to oil palm plantations.

What are the effects of globalization?

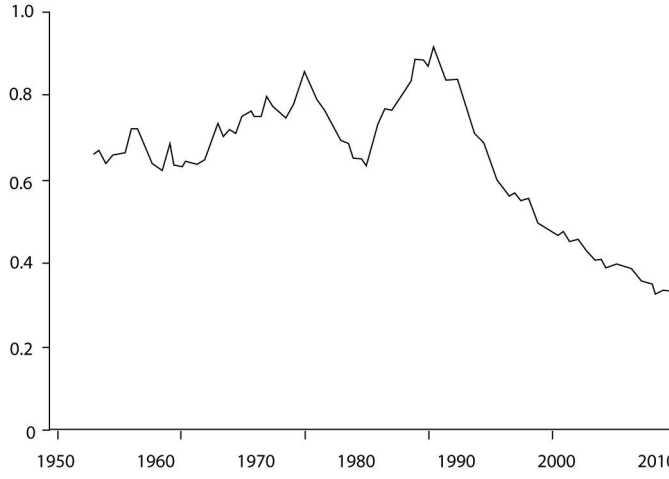
As noted above, the number of emerging and non-emerging infectious diseases has risen over the past century. At the same time, the number of outbreaks has also increased dramatically. The explanatory factors for these trends are associated with the global changes that continue to occur at an unprecedented speed and scale. These global

changes of anthropogenic origin impact biodiversity, which is undergoing a major crisis of extinction.

Biodiversity loss also applies to parasites themselves, which constitute more than half of all biological diversity (Morand *et al.*, 2015). Parasites are affected by the biodiversity crisis, even though their extinction rate is far from being accurately estimated (Dunn *et al.*, 2010). In developed countries, a sharp decline in parasite loads and the extinction of some human infectious diseases have been observed in the last century (Armstrong *et al.*, 1999). Finally, it is not so much the rise in the total number of human pathogens (including emerging pathogens) in the world over the past decades, but the increase in the number of infectious disease epidemics that makes the different (see Fig. 2).

The last decades stand out for the homogenization of parasitic diversity. This phenomenon appears to have started in the 1960s (Smith *et al.*, 2007), and is characterized by a striking homogenization of global epidemiological patterns. Countries are becoming much more similar in terms of their infectious disease epidemics, with these epidemics being increasingly shared in space and time among countries. Nowadays, epidemics link a larger number of countries that are geographically close or economically connected, as depicted by a network analysis (Fig. 7).

Figure 7. Temporal evolution of the global epidemiological pattern of infectious diseases.



A network analysis of epidemics shared by countries and by year showed that the number of clusters of countries sharing epidemics or the same infectious diseases decreased from the 1960s, whereas the total number of epidemics increased (see Fig. 2). More and more countries had similar infectious disease epidemic profiles (data from the GIDEON database, taken from Poisot *et al.*, 2015).

At the same time, there is a loss of the genetic diversity among parasites and pathogens. This loss is likely related to a decrease and homogenization of domesticated animals breeds selected for intensive breeding, resulting in an alarming decline of genetic resources (Rosenthal 2009). Globally distributed livestock parasites, such as *Trichinella* worms, tapeworms or *Toxoplasma* protists, show a growing standardization of their genetic diversity, reflecting both global trade and the global circulation of a few high-performing strains adapted to the homogenous genetic backgrounds of these domesticated animals (Rosenthal 2009).

The main conclusion of the second part of this chapter is that although global changes affect the conditions of emergence or local epidemics, the globalization of the economy and trade makes it possible for new EIDs to reach anywhere in the world (provided that the location is well-connected to the global network). However, this globalization is accompanied by a decrease in the global genetic diversity of pathogens and the homogenization of the epidemiological environments.

Conclusion: Is the next plague certain?

Human pathogen communities have been enriched by wildlife and animal domestication, but globalization affects the tempo and geography of epidemics because of major changes in the interactions amongst humans, animals, biodiversity and the environment. Evolution and human history have repeatedly provided exceptional conditions for pathogens to thrive. Ongoing changes are creating new opportunities for infectious diseases to emerge and take hold.

The spatialization of disease emergence, past or future, if not accompanied by the understanding of the socioecological mechanisms of disease transmission, would only designate countries or regions as sources or targets of new epidemic risks that should be contained. Disease contagion can be prevented if their socioecological causes are treated. The globalization of exchanges and new epidemiological connections should help better guide our surveillance and public health systems, not for the unimaginable, unpredictable new emergence, but rather for the predictable, which is to say the many infectious disease epidemics that are already becoming globalized.

Interestingly, while parasite biodiversity has declined in developed countries as a result of an effective public health policy, new health problems have emerged. Two final examples will illustrate this point.

The eradication of smallpox (obviously a good thing) has led our societies to abandon vaccination against this terrible disease. However, smallpox vaccination provided protection against other related viruses, and stopping smallpox vaccination has had the unexpected consequence of promoting new infections from related viruses such as monkeypox and other viruses harboured in rodents (Vorou *et al.*, 2008).

However, the decline of parasitic biodiversity appears to favour the emergence of autoimmune diseases. Ulcers caused by the bacterium *Helicobacter pylori* seem to be

linked to the disappearance of nematodes and tapeworms in many developed countries. The absence of a parasitic community interacting with the microbial community results in increased antimicrobial inflammatory responses, leading to the emergence of ulcers (Weinstock *et al.*, 2004). Improved hygiene due to modifying the parasitome and the microbiome increases allergies and autoimmune diseases (Parker *et al.*, 2012). Ironically, we face two new pandemic disease threats at the same time: infectious communicable diseases due to new emerging pathogens and noncommunicable diseases due to the disappearance of pathogens!

In exploring the ecological and biological mechanisms possibly associated with emergence potential, this chapter has emphasized the importance of our relationships with wild and domesticated animals. New emerging infectious diseases may be indicative of these ultimate contacts with biodiversity in a period of major crisis. But, in terms of public health, the worst may not be where we are looking. We may be witnessing the final outbreaks of infectious diseases emerging from wildlife, and the new emergence of non-infectious diseases are still to come with the biodiversity crisis.